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April 19, 2004

Marianne Lamont Horinko, Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 2216

Attn: Chemical Right-to-Know Program

Re: EPA comments on the Test Plan and Robust Data Summary for sec-Butyl Urea

Dear Administrator Horinko,

E. I. du Pont de Nemours & Company, Inc. received EPA's comments on the test plan and robust data summary for sec-Butyl Urea and is pleased to respond. We have considered the recommended revisions to the closed system intermediate justification, physiochemical data, environmental fate, ecological effects and health effects. We have revised our submittal as needed on the attached summary sheet. Also included with this submittal is a revised robust data summary.

Please feel free to contact me with any questions or concerns you may have with regards to this submission at Edwin.L.Mongan-1@usa.dupont.com or by phone at 302-773-0910.

Sincerely,

Edwin L. Mongan, III
Manager, Environmental Stewardship
DuPont Safety, Health & Environment

Cc: Charles Auer – U.S. EPA
Office of Pollution Prevention & Toxics
U. S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Sec-butyl Urea: Response to EPA Comments

Physiochemical Data

EPA comment: *Melting/Boiling Point*. For melting point and boiling point, a sublimation temperature was provided in the robust summaries. However, these data are questionable given the measured melting point values identified by EPA for 2 analogs. Testing is needed for melting point and boiling point using OECD Test Guideline 102 and 103, respectively.

Response: Since the data provided for sublimation temperature are measured data, testing for melting point and boiling point are not applicable.

EPA comment: *Vapor pressure.* An estimated vapor pressure was provided. According to HPV Challenge Program guidelines, this endpoint should be measured if the vapor pressure is likely to be $>10^{-5}$ Pa. The submitter should determine vapor pressure using OECD Test Guideline 104.

Response: The test plan has been updated to include the recommended vapor pressure test following OECD Test Guideline 104.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

EPA comment: *Photodegradation*. For photodegradation, no data were presented. The submitter needs to estimate the photooxidation potential of sec-butyl urea using AOPWIN.

Response: Data were added to the robust summary.

EPA comment: *Biodegradation*. For biodegradation, the submitter provided only an estimate of the biodegradation potential using BIOWIN. Ready biodegradation needs to be measured experimentally following OECD Test Guideline 301.

Response: The test plan has been updated to include the recommended biodegradation test following OECD Test Guideline 301.

Ecological Effects

EPA comment: No justification for the suitability of the analog was provided and ECOSAR values for sec-butyl urea and the analog differ by a factor of 10. Therefore, these data appear inadequate to satisfy the aquatic toxicity endpoints. Adequate justification needs to be submitted for the adequacy of the analog data; otherwise, acute fish, invertebrate, and algal toxicity testing on sec-butyl urea may be needed.

Response: Additional information was added to the robust summary.

Health Effects

EPA comment: EPA believes that additional justification is needed to support using data on isobutylidene diurea for addressing some of the health effects endpoints. The justification for using the analog is based on the formation of a common metabolite, 1-hydroxyisobutlyurea. While this is a reasonable hypothesis, no data are presented on the rate of metabolite formation or whether 100 percent of the parent compound would be metabolized to 1-hydroxyisobutylurea. Thus, one cannot judge whether to ascribe any observed toxicity to the metabolite or to the unmetabolized parent compound. For developmental toxicity, robust summaries need to be submitted on the structurally related alkyl ureas to allow a determination of data adequacy.

Response: Metabolism data was removed, and the additional requested analog data was added to the robust summary.

General Comment

EPA comment: Additional information is necessary to judge the "closed system intermediate" claim. In particular, a process flow diagram should be provided for each site where the material is handled. Although a narrative is provided for the manufacturing site, no description is provided of the processing site other than to say that the customer uses "adequate controls." Some monitoring data are provided, but it is not clear what operation/area was monitored. The following statements beg the question about the "closed system intermediate" claim: "Any spills that result from bag loading are washed down to the on-site biological treatment plant. Process wastes from the manufacture of SBU are also treated at the on-site biological treatment plant." Additional details need to be provided about the quantity of spilled material and process wastes and biological treatment efficiency.

Response: Additional information and details were added to the robust summary. Monitoring data has been updated to include an additional year of exposure data.

19 April 2004

ROBUST SUMMARY FOR SEC-BUTYL UREA

Summary

Sec-butyl urea is an odorless white crystalline solid with a measured sublimation point of 171°C, and an estimated boiling point of 224.95°C. Sec-butyl urea has a specific gravity of 0.25-0.28, and an estimated log Kow of 0.31. Sec-butyl urea has a water solubility value of 4 wt% at 20ºC. Only an estimated vapor pressure of 0.00294 mm Hg at 25ºC was available. According to the HPV Challenge Program guidelines, vapor pressure should be measured if the vapor pressure is likely to be greater than 10^{-5} Pa; therefore a test following OECD guideline 104 is recommended.

Modeled data rank sec-butyl urea as being of low environmental concern for stewardship and regulatory action, which results from a low persistence score and a low score for bioaccumulation using the standard EPA emissions scenario of equal emissions to air, water, and soil. Predicted half-life in sediment, 140 days, indicates moderate persistence in this environmental compartment, but the estimated distribution based on Level III fugacity modeling predicts that sec-butyl urea will not partition into this compartment under tested release scenarios. Water and soil are predicted to be the major environmental compartments into which sec-butyl urea will partition. Estimated hydrolysis rates in water are slow. Estimated biodegradation rates indicate that this is a more important decay process in water. However, to accurately predict the biodegradation potential of sec-butyl urea, a ready biodegradation test following OECD guideline 301 is recommended. A worst-case scenario was also determined using EPIWIN v. 3.05. The 100% emission to soil scenario resulted in the longest half-life in soil (34 days). This half-life was also in the low persistence range (<2 months).

ECOSAR (Meylan and Howard, 1999) was used to estimate the missing aquatic toxicity data for sec-butyl urea to fish, *Daphnia* (planktonic freshwater crustaceans), and algae. Based on the fact that sec-butyl urea is produced at only one DuPont site as an isolated intermediate[1] and ECOSAR predictions of an estimated 96-hour LC_{50} in fish of 1806 mg/L, an estimated 48-hour EC_{50} in *Daphnia* of 3184 mg/L, and an estimated 96-hour EC_{50} in green algae of 3339 mg/L, sec-butyl urea would be of low concern for toxicity to aquatic organisms. Substantiating these results are measured data and ECOSAR results for a structurally related compound, isobutylidene diurea (CAS# 6104-30-9). Measured aquatic toxicity data for this analog compound, as well as data estimated using ECOSAR, indicate that it is of low concern for toxicity to aquatic organisms. The difference in toxicity is related solely to the Kow of the compound. Given the agreement between ECOSAR and actual test data for the analog compound, and the low observed toxicity of the analog and predicted toxicity for sec-butyl urea, no additional aquatic testing is warranted.

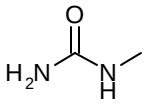
[1]As defined by EPA guidance, an isolated intermediate is one in which there is controlled transport, i.e. to a limited number of locations within the same company or second parties that use the chemical in a controlled way as an intermediate with a well known technology.

Compound	Algae, 96-hr EC_{50}	Daphnid, 48-hr EC_{50}	Fish, 96-hr LC_{50}
Sec-butyl urea	1806 mg/L[a]	3184 mg/L[a]	3339 mg/L[a]
Isobutylidene diurea	$1.56x10^5$ mg/L[b] >500 mg/L*	$3.09x10^5$ mg/L[b] >1000 mg/L*	$3.72x10^5$ mg/L[b] >1000 mg/L*
* Measured data. [a] Log_{10} Kow of 0.31 used for modeling. [b] Log_{10} Kow of –1.68 used for modeling.			

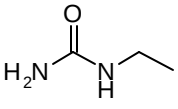
Sec-butyl urea has very low acute oral toxicity with an ALD of 7500 mg/kg in rats. Sec-butyl urea was a moderate eye irritant, producing temporary corneal injury, iritic congestion, and conjunctivitis when tested in rabbit eyes.

There is no developmental toxicity study available for SBU. Although the quantitative structure toxicity relationship (QSTR) model TOPKAT predicts that SBU would be a developmental toxin, literature on a closely related material suggests that SBU would not be a developmental toxin. When using such QSTR models, it is important to examine the training set of compounds from which the model is derived. The majority of the training set of structures the TOPKAT model is based upon thioureas that are known developmental toxins. One possible mechanism for the toxicity of thioureas is the formation of reactive sulfonyl metabolites during the oxidative desulfuration reaction. Under this mechanism, the corresponding ureas are not reactive, but are detoxification products of the thioureas. Therefore, using thioureas as the training set to build the QSTR model for the ureas is scientifically unsound and invalid.

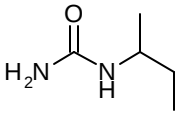
A study of the teratogenic effects of *N*-alkylureas (e.g., 1-methylurea, 1-ethylurea) found they are not teratogens, while their corresponding thioureas (1-methylthiourea and 1-ethylthiourea) are teratogenic (Teramoto et al., 1981). Using the closest neighbor analogy, we strongly believe that it is unlikely that SBU is a teratogen.



1-methylurea
(not a teratogen)



1 -ethylurea
(not a tetatogen)



sec-butylurea (SBU)

Based on the above scientific justification and using the scientific rationale consistent with the procedures described in the EPA Office of Pollution Prevention and Toxin technical document "The use of Structure-Activity Relationship (SAR) in the High Production Volume Chemical Challenge Program," no additional testing for developmental toxicity is necessary based on the following:

- **There is limited potential for exposure to SBU in quantities sufficient to produce effects**

SBU is a solid substance; the likelihood of exposure by the inhalation or dermal absorption route is negligible. It has very low toxicity by the oral route (rat oral ALD >7500 mg/kg). Information is presented that the potential for human contact in any substantial amount is quite low.

- **Alkyureas should not be grouped with alkylthioureas in the development of structure-toxicity activity relationship**

Teramoto et al., 1981 reported the relationship between the molecular structure of *N*-alkylureas and *N*-alkylthioureas and their teratogenic properties. Single maximum tolerated doses of 2000 mg/kg urea, methylurea, or ethylurea were given to pregnant rats on Day-12 of gestation. There were no significant differences from controls in mean number of implants, mean number of live fetuses, percent fetal resorptions, mean fetal weight, or percent malformed fetuses. In contrast, a number of these parameters were affected by the corresponding thioureas.

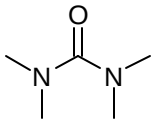
Two important observations were concluded:

1) The thiourea (C=S) moiety was essential for teratogenic potency.

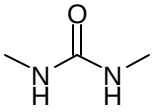
"There is one structural similarity between mono-alkylated thioureas and ETU which is essential for teratogenic potency. The C=S group is essential to mono-alklyated thioureas for manifesting teratogenic effects. Replacement of the C=S group with C=O (i.e., 1-methylurea or 1-ethylurea) resulted in the loss of teratogenicity."

2) The developmental toxicity of urea is related to the increasing number of methyl group attached.

Results from Teramoto's study are in agreement with the results reported by Von Kreybig et al., 1969, that "….teratogenic activity is enhanced by the increasing number of methyl group attached… 1,1,3,3-tetramethylurea , but not 1,3-dimethylurea, was teratogenic in rats…1,1,3,3-tetrametylurea is a strong teratogen toward the mouse fetus, where 1,3-dimethylurea was weak…."



1,1,3,3-tetramethylurea



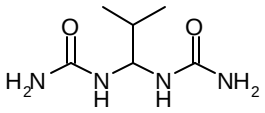
1,3-dimethylurea

The teratogenic effects of the thioureas and methylated ureas are different. "…Thioureas affects CNS where as methylated urea malformations are detected in the palate, tail, and extremities…" Furthermore, the effect observed with the ureas decreases with the increasing alkyl moiety..."

These two research findings support the conclusion that *sec*-butylurea is unlikely to be a teratogen/development toxin, based on structural similarity to methylurea, ethylurea, and 1,3-dimethylurea. In view of the above observations, it is unlikely that SBU will exhibit the CNS or structural malformation effects exhibited by both the thioureas and methylated ureas.

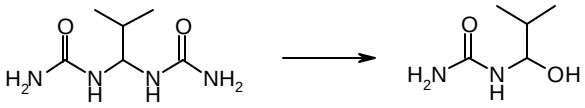
- **Studies with structurally related alkyl ureas show no developmental toxicity**

In addition to the study above in which rats were given large single doses during pregnancy, a traditional rat developmental study is available on isobutylidenediurea (IBDU, CAS #6104-30-9). The results of the developmental testing of IBDU are as follows. Wistar rats were given 0, 100, 400, or 1000 mg/kg IBDU in aqueous carboxymethyl cellulose suspension during days 6-15 of gestation (Hellwig, 1997; see also Section 6.3). There were no substance-related effects in dams (including body weight, body weight gain, food consumption, clinical signs of toxicity, or reproductive data) at any dose level tested. There was no increased incidence of fetal malformations, variations, or retardations at any dose level tested. Therefore, the no effect level for the maternal and developing organism was 1000 mg/kg/day, the highest dose tested. IBDU was not a developmental toxin in rats.



N, N"-(Isobutylidene)bisurea
N, N" -(Isobutylidene)diurea
N,N"-(2-Methylpropylidene)bisurea
CAS# 6104-30-9

N,N-(isobutylidene)diurea (IBDU) is a diurea that would be metabolized *in vivo* via an *N*-dealkylation reaction to yield 1-hydroxy isobutylurea (IBU-OH), a close structural analog of SBU.



IBDU IBU-OH

The close structural similarity between SBU and IBU also support the conclusion that SBU will be negative under same test condition as IBDU.

IBU SBU

IBDU/IBU can be considered as a suitable surrogate to testing SBU.

Related alkyl ureas that have been evaluated are not developmental toxins. One of the alkyl ureas already evaluated, and found not to be developmentally toxic is IBDU.

Lastly, reliance on existing studies would prevent unnecessary wastage of animals. Therefore, it can be concluded, based on existing literature, that SBU is unlikely to be developmentally toxic.

Therefore, DuPont proposes that no additional developmental toxicity testing is necessary for SBU based on available data for related materials. The physical nature of the material (solid and high water solubility) makes inhalation and dermal exposure unlikely. Since SBU is an industrial product not a consumer product, oral exposure is not expected.

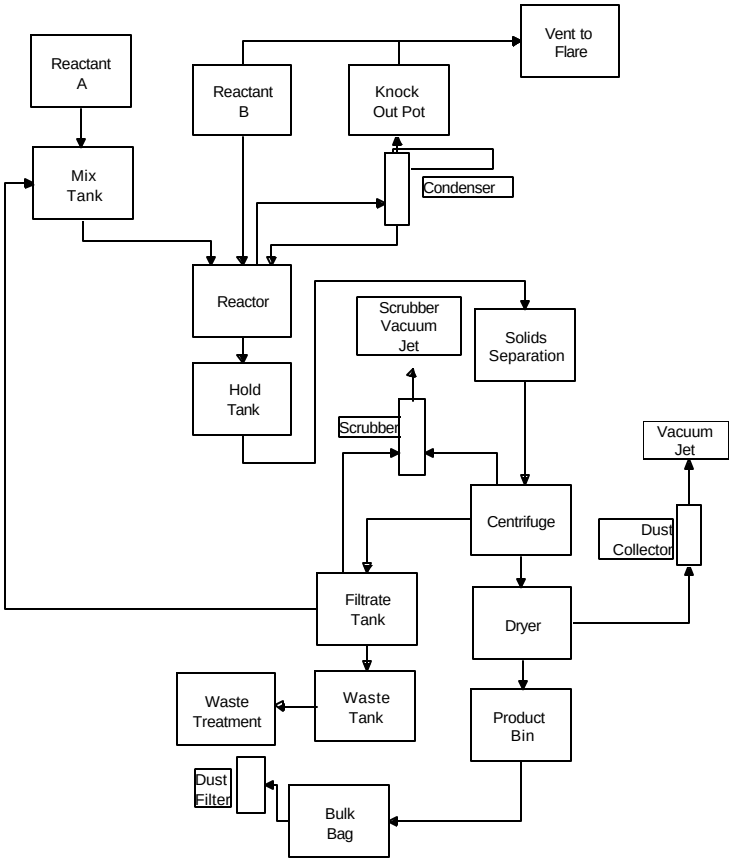
No genetic toxicity information was found. Therefore, an *in vitro* bacterial reverse mutation assay and *in vitro* clastogenicity study in human peripheral blood lymphocytes following OECD Guidelines 471 and 473, respectively are proposed.

As described below, the test material is an isolated intermediate; therefore, repeated dose and reproductive toxicity are not required.

Human Exposure

Sec-butyl urea, a white crystalline solid, is a chemical intermediate used in the production of a FIFRA registered herbicide. Sec-butyl urea (SBU) is manufactured at one DuPont facility (Belle Plant, WV), and is shipped overseas by bulk bag (333 kgs) to only one customer. 100% of the sec-butyl urea is sold into this application.

A process flow diagram for the DuPont SBU process is shown below.



SBU is made at the DuPont Belle Plant on a campaign basis (lasting several months) each year, as an isolated intermediate, with controlled transport to one other location within a second party that uses the chemical in a controlled way as an intermediate. The raw materials are mixed and reacted, then the product is filtered and dried. SBU is packed in bulk bags, placed on a cardboard sheet on pallets, and loaded in overseas shipping containers. There is no mixing of materials in the shipping containers, - they only contain SBU. Process wastes and cleanup waste from the manufacture of SBU are treated at the on-site biological treatment plant, which is covered under a NPDES permit with the state of West Virginia.

Dust is contained in the SBU production system in the following ways. The dust produced during drying is contained in a dust collector and returned to the dryer. The dryer is discharged

into a bin, which is vented through a vent sock filter. After each dryer batch is discharged, the dryer dump valve is cleaned. One to two SBU bulk bags are filled from each dryer batch. The bulk bag inlet is fitted over the charge nozzle. The bags are vented through a vent sock to capture dust during filling. Then the bag inlet is removed from the charge nozzle and the bag is closed. Cleaning the dryer door is performed approximately 5 times per shift, and 5 to 10 SBU bags are produced per shift. Due to the generally needle-like structure of the SBU crystals, SBU is less dusty than some materials. Potential for worker exposure to SBU during process operation and filling SBU bulk bags is characterized by the sampling results discussed at the end of this section.

Workers wear PPE as protection from leaks and spills when breaking lines or entering equipment for maintenance. This PPE consists of dust resistant gloves and goggles for breaking into lines. Equipment is normally wet-cleaned prior to entering equipment. However, if excessive dust is generated, a NIOSH approved air purifying respirator with particulate filters is worn.

The sites can have from 2 to 5 personnel working (construction, contractor, and plant employees). The areas where the substance is manufactured will have from 1 to 2 workers during normal operations and 4 to 10 people during a shutdown. Equipment is wet cleaned so that dust generation is minimized. The site that produces SBU has effective safety, health and environmental practices and procedures in addition to engineering controls, environmental controls, and personal protective equipment to control exposure. Adequate safety equipment, such as safety showers, eyewash fountains, and washing facilities, are available in the event of an occupational exposure. Individuals handling SBU should avoid contact with eyes, skin, or clothing, should not breathe dust, and should wash thoroughly after handling.

The only customer for SBU is located outside the US in Israel. This customer produced SBU from their own process for many years. SBU is stored by the customer in the bulk bags until charged to the reactor through a charge bin. All charging units are connected to a DCE dust collector. The dust collector filters are replaced between campaigns. DuPont conducted a contamination prevention audit at the customer's facility, and found that the customer's handling of the SBU included adequate controls.

Air monitoring has been conducted for the loading area of the DuPont Belle facility (SBU) and results are shown in the table below. LOGAN (lognormal analysis) is a computerized statistical method for characterizing occupational exposures to chemicals, noise, and other environmental hazards. LOGAN uses sequential collection of data and makes decisions on the minimum amount of data. It helps make cost-effective, accurate decisions that ensure a healthy workplace. LOGAN uses inferential statistics to estimate the true workplace conditions, in the same way that public polling estimates opinions by sampling a representative percentage of the public. LOGAN is designed to limit the risk of employee occupational overexposure to less than 5%.

Although a DuPont Acceptable Exposure Limit (AEL) has not been established for sec-butyl urea, the site uses a 10 mg/m^3, total dust, exposure limit for SBU based on an analogy to tertiary-Butylurea. The DuPont Acceptable Exposure Limit (AEL) for tertiary-Butylurea is 10 mg/m^3, total dust. Air monitoring has been conducted to characterize employee exposure to secondary-Butylurea (SBU) and results are shown in the table below. All measured

concentrations are well below the 10 mg/m^3 exposure limit, and the conclusion of the Logan analysis was "Acceptable". Results shown in the table below characterize exposure for those who perform SBU production job, including filling SBU bags and cleaning the dryer dump valve.

Exposure Data:

Job Sampled	No. of Results	Average (mg/m^3)	Minimum (mg/m^3)	Maximum (mg/m^3)
DuPont Manufacturing Site Workers (full shift)	**18***	**0.129**	**<0.1**	**0.4**

* For time period 1998-2003

References for Summary:

Hellwig, J. et al. (1997). Food Chem. Toxicol., 35:677-681.

Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).

Teramoto, S. et al. (1981). Teratology, 23:335-342.

Von Kreybig, T. et al. (1969). Arzneim. Forsch., 19:1073-1076.

19 April 2004

TEST PLAN FOR SEC-BUTYL UREA

Sec-butyl urea CAS No. 689-11-2	**Data Available**	**Data Acceptable**	**Testing Required**
Study	**Y/N**	**Y/N**	**Y/N**
PHYSICAL/CHEMICAL CHARACTERISTICS			
Melting Point	Y	Y	N
Boiling Point	Y	Y	N
Vapor Pressure	Y	Y	Y
Partition Coefficient	Y	Y	N
Water Solubility	Y	Y	N
ENVIRONMENTAL FATE			
Photodegradation	Y	Y	N
Stability in Water	Y	Y	N
Transport (Fugacity)	Y	Y	N
Biodegradation	Y	N	Y
ECOTOXICITY			
Acute Toxicity to Fish	Y[1]	Y	N
Acute Toxicity to Invertebrates	Y[1]	Y	N
Acute Toxicity to Aquatic Plants	Y[1]	Y	N
MAMMALIAN TOXICITY			
Acute Toxicity	Y	Y	N
Repeated Dose Toxicity	N/A	N/A	N/A
Developmental Toxicity	Y[2]	Y	N
Reproductive Toxicity	N/A	N/A	N/A
Genetic Toxicity Gene Mutations	N	N	Y
Genetic Toxicity Chromosomal Aberrations	N	N	Y

[1]Data for a related material, isobutylidene diurea, are available.
[2]Data for related materials, isobutylidene diurea, urea, methylurea, and ethylurea, are available.

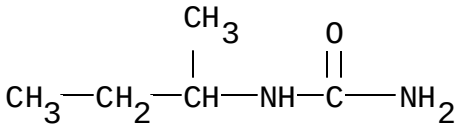
Existing published and unpublished data were collected and scientifically evaluated to determine the best possible study or studies to be summarized for each required endpoint. In the spirit of this voluntary program, other data of equal or lesser quality are not summarized, but are listed as related references at the end of each appropriate section, with a statement to reflect the reason why these studies were not summarized.

1.0 Substance Information

CAS Number: 689-11-2

Chemical Name: Urea, (1-methylpropyl)-

Structural Formula:



Other Names: Urea, sec-butyl-
N-sec-butylurea
Sec-butylurea
Secondary butylurea
Urea, 1-sec-butyl-

Exposure Limits: No Data.

2.0 Physical/Chemical Properties

2.1 Melting Point

Value:	No Data
Decomposition:	No Data
Sublimation:	171°C
Pressure:	No Data
Method:	No Data
GLP:	Unknown
Reference:	DuPont Co. (1979). Unpublished Data, "Sublimation Test with Sec-butyl urea" (January 19). DuPont Co. (1992). Material Safety Data Sheet No. B0000007 (November 17).
Reliability:	Not assignable because limited study information was available.

Additional References for Melting Point: None Found.

2.2 Boiling Point

Value:	224.95°C
Decomposition:	No Data
Pressure:	760 mm Hg
Method:	Modeled. MPBPWIN, v. 1.4 module of EPIWIN 3.05 (Syracuse Research Corporation). MPBPWIN estimates the normal boiling point using an adaptation of the Stein and Brown (1994) method, which is an extension and refinement of the Joback method (Joback, 1982; Reid et al., 1987).
GLP:	Not Applicable
Reference:	Stein, S. E. and R. L. Brown (1994). J. Chem. Inf. Comput. Sci., 34:581-587. Joback, K. G. (1982). A Unified Approach to Physical Property Estimation Using Multivariate Statistical Techniques. Stevens Institute of Technology, submitted to the Dept. of Chem. Eng. for M.S. Degree at the Massachusetts Institute of Technology in June 1984 (see also: Reid et al., 1987). Reid, R. C. et al. (1987). The Properties of Gases and Liquids. 4th edition, Chapter 2, McGraw-Hill, Inc., NY.
Reliability:	Estimated value based on accepted model.

Additional References for Boiling Point: None Found.

2.3 Density

Value:	Specific gravity = 0.25-0.28
Temperature:	No Data
Method:	No Data
GLP:	Unknown
Results:	No additional data.
Reference:	DuPont Co. (1992). Material Safety Data Sheet No. B0000007 (November 17).
Reliability:	Not assignable because limited study information was available.

Additional References for Density: None Found.

2.4 Vapor Pressure

Value:	0.00294 mm Hg
Temperature:	25°C
Decomposition:	No Data
Method:	Modeled. MPBPWIN, v. 1.4, module of EPIWIN 3.05 (Syracuse Research Corporation). MPBPWIN estimates vapor pressure (VP) by three separate methods: (1) the Antoine method, (2) the modified Grain method, and (3) the Mackay method. All three use the normal boiling point to estimate VP.
GLP:	Not Applicable
Reference:	Lyman, W. J. et al. (1990). Handbook of Chemical Property Estimation Methods, Chapter 14, American Chemical Society, Washington, DC. Lyman, W. J. (1985). In: Environmental Exposure From Chemicals, Volume I, Chapter 2, Neely, W. B. and G. E. Blau (eds.), CRC Press, Inc., Boca Raton, FL.
Reliability:	Estimated value based on accepted model.

Additional References for Vapor Pressure: None Found.

2.5 Partition Coefficient (log Kow)

Value:	0.31
Temperature:	25^{o}C
Method:	Modeled. KOWWIN, v. 1.66, module of EPIWIN 3.05 (Syracuse Research Corporation). KOWWIN uses "fragment constant" methodologies to predict log P. In a "fragment constant" method, a structure is divided into fragments (atom or larger functional groups) and coefficient values of each fragment or group are summed together to yield the log P estimate.
GLP:	Not Applicable
Reference:	Meylan, W. M. and P. H. Howard (1995). J. Pharm. Sci., 84:83-92.
Reliability:	Estimated value based on accepted model.

Additional References for Partition Coefficient (log Kow): None Found.

2.6 Water Solubility

Value:	4 WT%
Temperature:	20°C
pH/pKa:	No Data
Method:	No Data
GLP:	Unknown
Reference:	DuPont Co. (1992). Material Safety Data Sheet No. B0000007 (November 17).
Reliability:	Not assignable because limited study information was available.

Value:	10 WT%
Temperature:	60°C
pH/pKa:	No Data
Method:	No Data
GLP:	Unknown
Reference:	DuPont Co. (1992). Material Safety Data Sheet No. B0000007 (November 17).
Reliability:	Not assignable because limited study information was available.

Additional References for Water Solubility: None Found.

2.7 Flash Point: No Data.

2.8 Flammability

Value:	Lower Explosive Limit: 0.023 g/L Limiting Oxygen Concentration: >12% Minimum Ignition Energy: 20-50 mJ
Method:	A Hartmann Dust Tube was used to determine the lower explosive limit (LEL), limiting oxygen concentration (LOC), and minimum ignition energy (MIE). A weighed sample was placed into a cup at the base of a sealed stainless steel tube. A continuous AC arc was energized between 2 tungsten electrodes in the tube as a pulse of air dispersed the sample into a cloud. If the sample concentration was above the LEL, defined as the lowest dust concentration sufficient for sustained flame propagation, the arc would cause the material to deflagrate and the resulting pressure increase would be detected by a pressure transducer in the top of the tube. Pressure/time and rate/time measurements were recorded. LEL was reported as the highest dust concentration resulting in a "NO GO" (pressure increase

<1 psig over initial dispersion pressure).

The LOC, defined as the highest oxygen concentration permissible to prevent combustion for any dust concentration, was determined with a modified version of the above procedure. Ignition was attempted on dust samples of various concentrations that were dispersed by oxygen/nitrogen mixtures of known compositions. The sample was tested at decreasing oxygen levels until a point was reached where no combustion events were observed (pressure increase <1 psig over initial dispersion pressure) for any of the concentrations tested. This level was reported as the LOC.

The test method for MIE involved subjecting dust clouds of varying concentrations to electrical sparks of different energy levels. The test sample was placed in a sample cup at the base of an acrylic tube and was dispersed into a cloud by a blast of low pressure air. After a preset time delay to allow cloud formation, a low energy triggering spark was discharged between 2 electrodes to initiate discharge of a higher energy DC spark stored in a capacitor. A combustion event ("GO") was evidenced by observation of a flame accompanied by bursting of a full diameter paper rupture disc at the top of the tube. For a given energy level, tests were conducted at varying dust concentrations; if a "GO" event was obtained in 10 trials for any of the concentrations tested, the energy level was reduced and the tests repeated. This procedure was continued until and energy level was reached where no combustion events were observed in 10 trials for any of the concentrations tested. The MIE was then reported as being located between this energy level and the next highest energy level tested.

The LEL, LOC, and MIE values determined by these procedures are valid for atmospheric pressure and ambient temperature only.

GLP: Unknown

Reference: DuPont Co. (1995). Unpublished Data, "Dust Explosivity Characteristics of Sec-butyl Urea" (July 18).

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for Flammability:

DuPont Co. (1992). Material Safety Data Sheet No. B0000007 (November 17).

3.0 Environmental Fate

3.1 Photodegradation

Concentration:	No Data
Temperature:	No Data
Direct Photolysis:	No Data, but inspection of the chemical structure indicates that sec-butyl urea does not contain structural fragments typically subject to aqueous photolysis.
Indirect Photolysis:	The rate constant for reaction with OH radicals = 13.2668×10^{-12} cm^3/molecule-sec (24-hour day; 0.5×10^6 OH/cm^3) yielding an estimated half-life of 29.024 hours.
Breakdown Products:	No Data
Method:	Direct Photolysis: Inspection of chemical structure. Indirect Photolysis: Modeled. AOPWIN, v1.91 module of EPIWIN 3.11.
GLP:	Not Applicable
Reference:	Harris, J. C. (1990). Rate of Aqueous Photolysis, Chapter 8, In: Lyman, W. J. et al. (eds.). Handbook of Chemical Property Estimation Methods, American Chemical Society, Washington, DC. Indirect Photolysis: Meylan, W. M. and P. H. Howard (1993). Chemosphere, 26:2293-2299.
Reliability:	Estimate based on known qualitative structure-activity relationships.

Additional References for Photodegradation: None Found.

3.2 Stability in Water

Concentration:	No Data
Half-life:	No value. The estimated rate of hydrolysis is extremely slow, beyond the typical range for quantitative model estimates.
% Hydrolyzed:	No Data
Method:	Modeled. HYDROWIN, v. 1.67 module of EPIWIN v3.05 (Syracuse Research Corporation). HYDROWIN estimates aqueous hydrolysis rate constants for the following chemical classes: esters, carbamates, epoxides, halomethanes and selected alkyl halides. HYDROWIN estimates acid- and base-catalyzed rate constants; it does NOT estimate neutral hydrolysis rate constants. The prediction methodology was developed for the U.S. Environmental Protection Agency and is outlined in Mill et al., 1987.

GLP:	Not Applicable
Reference:	Mill, T. et al. (1987). "Environmental Fate and Exposure Studies Development of a PC-SAR for Hydrolysis: Esters, Alkyl Halides and Epoxides," EPA Contract No. 68-02-4254, SRI International, Menlo Park, CA.
Reliability:	Estimated value based on accepted model.

Additional References for Stability in Water: None Found.

3.3 Transport (Fugacity)

Media:	Air, Water, Soil, and Sediments	
Distributions:	Air:	0.0594%
	Water:	44.6%
	Soil:	55.2%
	Sediment:	0.0757%
Half-life:	Air:	29 hours
	Water:	360 hours
	Soil:	360 hours
	Sediment:	1.44×10^3 hours
Adsorption Coefficient:	Estimated log Koc = 0.84	
Desorption:	Not Applicable	
Volatility:	Not Applicable	
Method:	Modeled.	

Henry's Law Constant - HENRYWIN v. 3.10 module of EPIWIN v3.05 (Syracuse Research Corporation). Henry's Law Constant (HLC) is estimated by two separate methods that yield two separate estimates. The first method is the bond contribution method and the second is the group contribution method. The bond contribution method is able to estimate many more types of structures; however, the group method estimate is usually preferred (but not always) when all fragment values are available.

Log Koc – Calculated from log Kow by the Mackay Level III fugacity model incorporated into EPIWIN v3.05 (Syracuse Research Corporation).

Environmental Distribution - Mackay Level III fugacity model, in EPIWIN v3.05 (Syracuse Research Corporation). Emissions (1000 kg/hr) to air, water, and soil compartments and the following input values:

Molecular Weight: 116.16
Henry's Law Constant: 1.87×10^{-9} atm-m^3/mole

(HENRYWIN program)
Vapor Pressure: 0.00294 mm Hg (MPBPWIN program)
Melting Point : 171°C (user-entered)
Log Kow: 0.31 (KOWWIN program)
Soil Koc: 0.837 (calculated by Level III model)

GLP: Not Applicable

References: HENRYWIN

Hine, J. and P. K. Mookerjee (1975). J. Org. Chem., 40(3):292-298.

Meylan, W. and P. H. Howard (1991). Environ. Toxicol. Chem., 10:1283-1293.

Fugacity - The methodology and programming for the Level III fugacity model incorporated into EPIWIN v3.05 (Syracuse Research Corporation) were developed by Dr. Donald MacKay and coworkers and are detailed in:

Mackay, D. (1991). Multimedia Environmental Models: The Fugacity Approach, pp. 67-183, Lewis Publishers, CRC Press.

Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1618-1626.

Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1627-1637.

Reliability: Estimated value based on accepted model.

Additional Reference for Transport (Fugacity):

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

SRC (Syracuse Research Corporation) (1988). Syracuse Research Corporation Calculated Values (NISC/EF-0007592).

3.4 Biodegradation

Value: Ultimate Biodegradation Timeframe: Weeks. This indicates that sec-butyl urea is expected to be readily biodegradable. The equivalent half-life for the Weeks timeframe is 15 days. Using a first order model, 70% of theoretical oxygen demand would occur in about 26 days.

Breakdown No Data

Products:	
Method:	Modeled. BIOWIN, v. 4.0 module of EPINWINN v3.05 (Syracuse Research Corporation). BIOWIN estimates the probability for the rapid aerobic biodegradation of an organic chemical in the presence of mixed populations of environmental microorganisms. Estimates are based upon fragment constants that were developed using multiple linear and non-linear regression analyses.
GLP:	Not Applicable
Reference:	Boethling, R. S. et al. (1994). Environ. Sci. Technol., 28:459-65. Howard, P. H. et al. (1987). Environ. Toxicol. Chem., 6:1-10. Howard, P. H. et al. (1992). Environ. Toxicol. Chem., 11:593-603. Tunkel, J. et al. (2000). Predicting Ready Biodegradability in the MITI Test. Environ. Toxicol. Chem., accepted for publication.
Reliability:	Estimated value based on accepted model.

Additional References for Biodegradation: None Found.

3.5 Bioconcentration

Value:	BCF = 3.162 (log BCF = 0.500). This BCF value suggests that bioconcentration potential in aquatic organisms is low.
Method:	Modeled. BCFWIN v. 2.4 module of EPINWINN v3.05 (Syracuse Research Corporation). BCFWIN estimates the bioconcentration factor (BCF) of an organic compound using the compound's log octanol-water partition coefficient (Kow) with correction factors based on molecular fragments.
GLP:	Not Applicable
Reference:	"Improved Method for Estimating Bioconcentration Factor (BCF) from Octanol-Water Partition Coefficient," SRC TR-97-006 (2nd Update), July 22, 1997; prepared for Robert S. Boethling, EPA-OPPT, Washington, DC, Contract No. 68-D5-0012; prepared by William M. Meylan, Philip H. Howard, Dallas Aronson, Heather Printup, and Sybil Gouchie, Syracuse Research Corp.
Reliability:	Estimated value based on accepted model.

Additional References for Bioconcentration: None Found.

4.0 Ecotoxicity

4.1 Acute Toxicity to Fish

Type:	**96-hour LC_{50}**
Species:	Fish
Value:	3339 mg/L (using $\log_{10}$ Kow of 0.31)
Method:	Modeled
GLP:	Not Applicable
Test Substance:	Sec-butyl urea
Results:	No additional data.
Reference:	Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).
Reliability:	Estimated value based on accepted model.

Type:	**96-hour LC_{50}**
Species:	*Salmo gairdneri* (rainbow trout)
Value:	>1000 mg/L
Method:	OECD Guideline 203, "Fish, Acute Toxicity Test" (1984). No additional information was reported.
GLP:	No
Test Substance:	Isobutylidene diurea, purity 88%
Results:	The LC_{50} was calculated based on nominal test concentrations. The NOEC, LC_0, and LC_{100} were 1000, 1000, and >1000 mg/L, respectively. No additional information was reported.
Reference:	BASF AG (1986). Department of Toxicology, Unpublished investigation (86/173), 19.12.1986 (cited in IUCLID (2000). IUCLID Dataset, "N,N"-(isobutylidene)diurea" (February 18, 2000)).
Reliability:	Medium because a suboptimal study design for testing (nominal test concentrations) was used.

Type:	**96-hour LC_{50}**
Species:	Fish
Value:	3.72×10^5 mg/L (using $\log_{10}$ Kow of –1.68)
Method:	Modeled
GLP:	Not Applicable
Test Substance:	Isobutylidene diurea
Results:	No additional data.
Reference:	Meylan, W. M. and P. H. Howard (1999). User's Guide for

	the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).
Reliability:	Estimated value based on accepted model.

Additional References for Acute Toxicity to Fish: None Found.

4.2 Acute Toxicity to Invertebrates

Type:	**48-hour EC_{50}**
Species:	*Daphnia*
Value:	3184 mg/L (log_{10} Kow of 0.31)
Method:	Modeled
GLP:	Not Applicable
Test Substance:	Sec-butyl urea
Results:	No additional data.
Reference:	Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).
Reliability:	Estimated value based on accepted model.

Type:	**48-hour EC_{50}**
Species:	*Daphnia magna*
Value:	>1000 mg/L
Method:	Directive 84/449/EEC, C.2 "Acute toxicity for *Daphnia*." No additional information was reported.
GLP:	Unknown
Test Substance:	Isobutylidene diurea, purity not reported
Results:	The EC_{50} was calculated based on nominal test concentrations. The 48-hour EC_0 and EC_{100} were 250 and >500 mg/L, respectively. The 24-hour EC_0, EC_{50}, and EC_{100} were 500, >500, and >500 mg/L, respectively. No additional information was reported.
Reference:	BASF AG (1987). Ecology Laboratory, Unpublished investigation (1108/87) (cited in IUCLID (2000). IUCLID Dataset, "N,N"-(isobutylidene)diurea" (February 18)).
Reliability:	Medium because a suboptimal study design for testing (nominal test concentrations) was used.

Type:	**48-hour EC_{50}**
Species:	*Daphnia*
Value:	$3.09x10^5$ mg/L (log_{10} Kow of –1.68)
Method:	Modeled
GLP:	Not Applicable
Test Substance:	Isobutylidene diurea
Results:	No additional data.
Reference:	Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).
Reliability:	Estimated value based on accepted model.

Additional References for Acute Toxicity to Invertebrates: None Found.

4.3 Acute Toxicity to Aquatic Plants

Type:	**96-hour EC_{50}**
Species:	Algae
Value:	1806 mg/L (log_{10} Kow of 0.31)
Method:	Modeled
GLP:	Not Applicable
Test Substance:	Sec-butyl urea
Results:	No additional data.
Reference:	Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).
Reliability:	Estimated value based on accepted model.

Type:	**96-hour EC_{50}**
Species:	*Scenedesmus subspicatus* (algae)
Value:	>500 mg/L
Method:	DIN 38412 Part 9, "*Scenedsmus*-cell multiplication inhibition test, regulation of the inhibition effect of substances contained in water on green algae." No additional information was reported.
GLP:	Unknown
Test Substance:	Isobutylidene diurea, purity not reported
Results:	The EC_{50} was calculated based on nominal test

concentrations. The 96-hour EC_{20} was >500 mg/L. The 72-hour EC_{20} and EC_{50} were 500 and >500 mg/L, respectively. No additional information was reported.

Reference: BASF AG (1987). Ecology Laboratory, Unpublished investigation (1108/87) (cited in IUCLID (2000). IUCLID Dataset, "N,N"-(isobutylidene)diurea" (February 18)).

Reliability: Medium because a suboptimal study design for testing (nominal test concentrations) was used.

Type: **96-hour EC_{50}**
Species: Algae
Value: $1.56x10^5$ mg/L (log_{10} Kow of –1.68)
Method: Modeled
GLP: Not Applicable
Test Substance: Isobutylidene diurea
Results: No additional data.
Reference: Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).
Reliability: Estimated value based on accepted model.

Additional References for Acute Toxicity to Aquatic Plants: None Found.

5.0 Mammalian Toxicity

5.1 Acute Toxicity

Type: **Oral ALD**
Species/Strain: Male rats/ChR-CD
Value: 7500 mg/kg
Method: No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

The test substance was administered by intragastric intubation as a suspension in peanut oil in single doses of 670, 2250, 3400, 5000, 7500, 11,000, and 17,000 mg/kg to young adult male rats. Survivors were sacrificed 14 days later. Pathological examination was performed on the survivors.
GLP: No
Test Substance: sec-Butyl urea, purity 90%

Results:	Mortality was 0/1, 0/1, 0/1, 0/2, 2/3, 0/2, and 1/2 at 670, 2250, 3400, 5000, 7500, 11,000, and 17,000 mg/kg, respectively. Mortality occurred within 2-3 days after dosing. Toxic signs observed at lethal doses included weight loss, red extremities, incoordination, lacrimation, prostration, and white precipitate from urine. Toxic signs at non-lethal doses were observed up to 2 days after dosing and included slight weight loss initially at =2250 mg/kg; red extremities, unresponsiveness, and incoordination at =3400 mg/kg; and white precipitate from the urine in 1 of 2 rats receiving 5000 mg/kg. At non-lethal doses, no pathologic changes that could be attributed to the test substance were observed in the tissues of rats that were sacrificed 14 days after treatment.
Reference:	DuPont Co. (1964). Unpublished Data, Haskell Laboratory Report No. 25-64, "Acute Oral Test" (March 3) (also cited in TSCA Fiche OTS0571269).
Reliability:	High because a scientifically defensible or guideline method was used.

Additional Reference for Acute Oral Toxicity:

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

DuPont Co. (1963). Unpublished Data, Haskell Laboratory Report No. 99-63, "Acute Oral Test" (September 26) (also cited in TSCA Fiche OTS0571577).

Type:	**Acute Inhalation Toxicity:** No Data.
Type:	**Acute Dermal Toxicity:** No Data.
Type:	**Dermal Irritation:** No Data.
Type:	**Dermal Sensitization:** No Data.
Type:	**Eye Irritation**
Species/Strain:	Rabbits/Strain not reported
Method:	No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study. Ten mg of the test substance, as powder, was sprinkled into the conjunctival sacs of 2 rabbit eyes. In addition, 0.1 mL of a 10% solution of the test substance in propylene glycol was instilled into the conjunctival sacs of another 2 rabbit eyes.

	One eye of each pair was irrigated with tap water 20 seconds after contact for a 1-minute interval. The other eye of each pair was not washed.
GLP:	No
Test Substance:	sec-Butyl urea, purity 100%
Results:	In the eye that was treated with the powder and washed after treatment, mild corneal injury through 1 day, mild congestion in the iris on the day of treatment, moderate swelling of the conjuctiva at 4 hours, and mild conjunctival irritation through 1 day were observed. In the eye not washed after treatment, moderate localized corneal injury for 2 days, marked congestion of the iris through 1 day, marked conjunctival swelling at 4 hours, and moderate conjunctival irritation at 1 day were observed. The conjunctival irritation diminished through 4 days, and the eye was normal by 7 days. In the eye that was treated with 0.1 mL 10% solution, no corneal injury, mild congestion through 1 day, and moderate conjunctival irritation on the day of treatment were observed in both treated eyes. The conjuctival irritation was mild through 1 day. Applying the current EPA eye scoring criteria, sec-butyl urea would be classified as Toxicity Category III, moderate eye irritant, based on corneal involvement clearing in 7 days or less.
Reference:	DuPont Co. (1963). Unpublished Data, Haskell Laboratory Report No. 99-63 "Eye Irritation Test" (September 26) (also cited in TSCA Fiche OTS0571577).
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Eye Irritation: None Found.

5.2 Repeated Dose Toxicity: Isolated Intermediate; Not a Required Endpoint.

5.3 Developmental Toxicity

Although no data for sec-butylurea exists, data available for structurally similar compounds (isobutylenediurea, urea, 1-ethylurea, 1-methyl urea, and 1,3-dimethyl urea) are summarized below.

SUPPOPRTING DATA: Isobutylenediurea

Species/Strain:	Rats/Wistar
Sex/Number:	Female/25 per group
Route of Administration:	Gavage
Exposure Period:	Days 6-15 post-coitum; Cesarean section on Day 20 post-coitum
Frequency of Treatment:	Daily
Exposure Levels:	0, 100, 400, 1000 mg/kg
Method:	The procedure used in the test was based on the recommendations of the following guidelines:

Commission Directive 87/302/EEC of 18 November 1987 adapting to technical progress for the 9th time Council Directive 67/548/EEC;

OECD Guideline No. 414;

EPA/FIFRA Pesticide Assessment Guidelines, Subdivision F, NTIS, §83-3, November 1984; and

Testing Guidelines for Toxicology Studies, Japan/MAFF, 1985.

A re-analysis of the stability of the test substance was performed on completion of the study. Analytical verifications of the stability of the IBDU suspensions in 0.5% aqueous carboxymethyl cellulose solution for up to 3 hours after preparation were performed. For verification of the concentrations, samples of the suspensions were twice analyzed by HPLC during the study period. At the beginning of the dosing period, samples were also used to verify the homogeneity of the 100 and 1000 mg/kg/day concentrations.

One to 4 female rats (65-74 days old; mean body weight of approximately 225 g) were mated with 1 male. The day on which sperm was detected in the vaginal smear was defined

as Day 0, and the following day as day 1 post-coitum (p.c.). Suspensions of IBDU in 0.5% aqueous carboxymethyl cellulose solution were freshly prepared before oral administration at a volume of 10 mL/kg body weight. All dams were weighed on days 0, 1, 3, 6, 8, 10, 13, 15, 17, and 20 p.c. With the exception of day 0, food consumption was recorded on the same days as body weight. On day 20 p.c. the dams were killed and given a gross autopsy. Body weight changes were determined and the corrected body weight gains were calculated. Intact uterine weight, number of corpora lutea, and number of implants (differentiated into live fetuses, dead implants, early and late resorptions, and dead fetuses) were recorded. The conception rate and pre- and post-implantation losses were calculated.

Fetuses were weighed and examined for external alterations, and sex was determined. Soft tissue examinations were performed on approximately 50% of fetuses after fixation in Bouin's solution, according to the method of Barrow and Taylor, 1969. Fetuses that did not receive a soft tissue examination were fixed in ethyl alcohol, stained, and examined for skeletal alterations.

Dunnett's test was used for statistically evaluating food consumption, body weight, body weight changes, corrected body weight gain, intact uterine weight, fetal and placental weights, the number of corpora lutea, implants, resorptions, live fetuses, and pre-or post-implantation losses. Fisher's exact test was used to evaluate the conception rate, maternal mortality, and all fetal findings.

GLP: Yes

Test Substance: Isobutylidenediurea, purity 90%

Results: The content of active ingredient was 90% prior to the beginning of the study. The re-analysis on its completion confirmed the tentative conclusion the suspensions were stable over a period of 3 hours at room temperature. It was also concluded that the prepared concentrations and the homogenous distribution of the test substance in the carrier were correct.

Pregnancy ratios were 23/25, 22/25, 22/25, and 24/25 at 0, 100, 400, and 1000 mg/kg/day, respectively. There were no mortalities or early deliveries observed at any dose level. No test substance-related effects on body weight, body weight gain, corrected body weight gain, food consumption, clinical signs, mean uterine weights, or gross pathological findings

were observed. No test substance-related differences in conception rate, mean number of corpora lutea, implantation sites, values calculated for pre- and post implantation loss, number of resorptions, or viable fetuses were observed. There was no effect on sex ratio, mean placental weight, or mean fetal weight. A summary of other reproductive outcomes (means/litter) are provided in the table below:

Concentration (ppm)	0	100	400	1000
Corpora Lutea:	16.8	15.5	15.8	15.7
Implantations:	15.7	14.5	14.3	14.4
% Pre-implantation loss:	6.7	6.3	10.0	9.8
Dead implants	0.8	1.0	1.1	0.9
% Post-implantation loss:	5.2	7.3	8.6	6.1
Total No. of Live Fetuses:	14.9	13.6	13.2	13.5
Mean Fetal Weight (g):	3.8	3.9	4.0	3.9
Sex Ratio (male:female):	52.8:47.2	53.2:46.8	53.3:46.7	48.3:51.7

Increased incidences of 2 skeletal malformations were unrelated to treatment. The overall malformation rate of the fetal skeletons was statistically significantly increased only in the 100 and 400 mg/kg/day dose groups. The differences observed between these treatment groups and the control fetuses were judged incidental since the frequency of dumbbell-shaped thoracic vertebral body/bodies (asymmetrical) and/or bipartite sternebra(e) with dislocated ossification centers was unusually low in the concurrent control group. Moreover, the slightly, albeit statistically significantly increased number of fetuses at 100 mg/kg/day with skeletal variations was interpreted as being spontaneous due to the lack of a dose-response relationship. Concerning fetal external, soft tissue, and skeletal findings, all differences observed between the control and the treated groups appeared without a clear dose-response relationship and were therefore judged as being without biological relevance. All the relevant findings occurred at incidences that were all within the range of historical control data.

A summary of statistically significant fetal anomalies are provided in the table below. Data are presented as number of fetuses (litters) affected.

Concentration (ppm)	0	100	400	1000
Skeletal, Number examined	177(23)	156(22)	151(22)	168(24)
Thoracic vertebral body/bodies dumbbell shaped (asymmetrical)	0(0)	5(4)	10(7)	5(4)
Sternebra(e) bipartite, ossification centers dislocated	0(0)	1(1)	4(3)	2(2)
Total fetal skeletal malformations	2(2)	9(7)	15(10)	7(5)

Thus there was no indication of IBDU-induced embryo/fetotoxicity or teratogenicity in Wistar rats, even at the highest dose. The NOAEL for the maternal and developing organism was 1000 mg/kg/day.

Reference: Hellwig, H. et al. (1997). Food Chem. Toxicol., 35:677-681.

Reliability: High because a scientifically defensible or guideline method was used.

SUPPORTING DATA: Urea

Species/Strain: Rats/Wistar
Mice/ICR

Sex/Number: Female/4 rats, 3 mice per dose level

Route of Administration: Gavage

Exposure Period: Rats: Gestation Day 12
Mice: Gestation Day 10

Frequency of Treatment: Single oral dose

Exposure Levels: Rats: 2000 mg/kg
Mice: 1000, 2000 mg/kg

Method: Rats and mice at 15 and 8 weeks of age, respectively, were used. They were housed in a controlled environment of 24±1°C and 55±5% relative humidity, maintained on laboratory chow, and given tap water *ad libitum*. Female rats and mice were paired overnight with a male, and were examined the following morning for the presence of vaginal plug (Day 0 of gestation).

Aqueous solutions of the test substances were prepared and given orally to female rats by intubation on day 12 of pregnancy, and on day 10 of pregnancy to female mice. Female rats and mice were killed on days 20 and 18 of pregnancy, respectively. The number of implants and live and dead fetuses were counted. Live fetuses were

	individually weighed and examined for gross abnormalities, and then divided into 2 groups. One group (derived from the right uterine horn) was processed for skeletal examinations. The other group was fixed in Bouin's and examined for visceral anomalies. Differences in numbers of implants, live fetuses, and fetal body weights were analyzed by the Student's t test. The litter was considered the experimental unit. Differences in resorption and malformation incidences, assessed on the basis of number of affected fetuses, were analyzed by the Chi-square test.
GLP:	Unknown
Test Substance:	Urea, purity not reported
Results:	Urea had no observable effect on fetal development in either rats or mice. Fetal survival and fetal weights were comparable to controls.
Reference:	Teramoto S. et al. (1981). Teratology, 23:335-342. Kaneda, M. et al. (1980). Teratology, 22(1):13A.
Reliability:	Medium because a suboptimal study design was used.
Species/Strain:	Rats/Wistar
Sex/Number:	Female/Number not reported
Route of Administration:	Gavage
Exposure Period:	14 days starting on the 6th day after last estrus
Frequency of Treatment:	2 times daily, half of the dose each time
Exposure Levels:	5000 mg/kg
Method:	No Data.
GLP:	Unknown
Test Substance:	Urea, purity not reported
Results:	Maternal toxicity included indications of apathy and loss of appetite. Plasma urea 1 hour post application was 1000 mg%, and 12 hours post application was 100 mg%. The young animals were examined before 48 hours post partum. Except for a slightly reduced birth weight no effects were found, especially on the kidneys there were no specific findings.
Reference:	Spielt, H. et al. (1969). Z. Urol. Nephrol., 68:623-627 (cited in IUCLID (2000). IUCLID Dataset, "Urea" (February 18)).
Reliability:	Medium because a suboptimal study design was used.

SUPPORTING DATA: Methylurea

Species/Strain:	Rats/Wistar Mice/ICR
Sex/Number:	Female rats/6 Female mice/ 10
Route of Administration:	Gavage
Exposure Period:	Rats: Gestation Day 12 Mice: Gestation Day 10
Frequency of Treatment:	Single oral dose
Exposure Levels:	Rats: 2000 mg/kg Mice: 2000 mg/kg
Method:	Rats and mice at 15 and 8 weeks of age, respectively, were used. They were housed in a controlled environment of 24±1°C and 55±5% relative humidity, maintained on laboratory chow, and given tap water *ad libitum*. Female rats and mice were paired overnight with a male, and were examined the following morning for the presence of vaginal plug (Day 0 of gestation). Aqueous solutions of the test substances were prepared and given orally to female rats by intubation on day 12 of pregnancy, and on day 10 of pregnancy to female mice. Urea and thiourea were used as negative controls. Female rats and mice were killed on days 20 and 18 of pregnancy, respectively. The number of implants and live and dead fetuses were counted. Live fetuses were individually weighed and examined for gross abnormalities, and then divided into 2 groups. One group (derived from the right uterine horn) was processed for skeletal examinations. The other group was fixed in Bouin's and examined for visceral anomalies. Differences in numbers of implants, live fetuses, and fetal body weights were analyzed by the Student's t test. The litter was considered the experimental unit. Differences in resorption and malformation incidences, assessed on the basis of number of affected fetuses, were analyzed by the Chi-square test.
GLP:	Unknown
Test Substance:	Methylurea, purity not reported
Results:	Methylurea had no observable effect on fetal development in either rats or mice. Fetal survival and fetal weights were comparable to controls.

Reference:	Teramoto S. et al. (1981). Teratology, 23:335-342.
	Kaneda, M. et al. (1980). Teratology, 22(1):13A.
Reliability:	Medium because a suboptimal study design was used.

SUPPORTING DATA: Ethylurea

Species/Strain:	Mice/ICR
Sex/Number:	Female/Number not reported
Route of Administration:	Diet
Exposure Period:	Gestation days 6-15
Frequency of Treatment:	*Ad libitum*
Exposure Levels:	0, 6000 mg/kg
Method:	Pregnant mice were given food, which contained ethylurea. The dams were killed on gestational day 18 and examined for maternal and embryo toxicity.
GLP:	Unknown
Test Substance:	Ethylurea, purity not reported
Results:	Ethylurea had no effect on maternal reproduction and fetal development. No further details were provided.
Reference:	Shimada, T. (1988). Teratology, 38(5):503.
Reliability:	Medium because limited study information was available.

Species/Strain:	Rats/Wistar Mice/ICR
Sex/Number:	Female rats/6 Female mice/12
Route of Administration:	Gavage
Exposure Period:	Rats: Gestation Day 12 Mice: Gestation Day 10
Frequency of Treatment:	Single oral dose
Exposure Levels:	Rats: 2000 mg/kg Mice: 2000 mg/kg
Method:	Rats and mice at 15 and 8 weeks of age, respectively, were used. They were housed in a controlled environment of 24±1°C and 55±5% relative humidity, maintained on laboratory chow, and given tap water *ad libitum*. Female rats and mice were paired overnight with a male, and were examined the following morning for the presence of vaginal plug (Day 0 of gestation). Aqueous solutions of the test substances were prepared and given orally to female rats by intubation on day 12 of

	pregnancy, and on day 10 of pregnancy to female mice. Urea and thiourea were used as negative controls. Female rats and mice were killed on days 20 and 18 of pregnancy, respectively. The number of implants and live and dead fetuses were counted. Live fetuses were individually weighed and examined for gross abnormalities, and then divided into 2 groups. One group (derived from the right uterine horn) was processed for skeletal examinations. The other group was fixed in Bouin's and examined for visceral anomalies. Differences in numbers of implants, live fetuses, and fetal body weights were analyzed by the Student's t test. The litter was considered the experimental unit. Differences in resorption and malformation incidences, assessed on the basis of number of affected fetuses, were analyzed by the Chi-square test.
GLP:	Unknown
Test Substance:	Ethylurea, purity not reported
Results:	Ethylurea had no observable effect on fetal development in either rats or mice. Fetal survival and fetal weights were comparable to controls. In the group of mice treated with ethylurea, a lower value in the number of implants led to a significant decrease n the number of live fetuses.
Reference:	Teramoto S. et al. (1981). Teratology, 23:335-342. Kaneda, M. et al. (1980). Teratology, 22(1):13A.
Reliability:	Medium because a suboptimal study design was used.

SUPPORTING DATA: 1,3-Dimethylurea

Species/Strain:	Rat/Wistar
Sex/Number:	Female/Number not reported
Route of Administration:	Gavage
Exposure Period:	Days 6-15 of gestation
Frequency of Treatment:	Once daily
Exposure Levels:	0, 30, 100, 200 mg/kg
Method:	OECD Guideline 414, "Teratogenicity."
GLP:	Yes
Test Substance:	1,3-Dimethylurea, purity not reported
Results:	Maternal toxicity was observed at $\geq$ 100 mg/kg, as evidenced by reduced body weight and food consumption. At 200 mg/kg, clearly reduced placenta weight and fetal body weight were observed. Fetuses in this dose group had increased incidences of hydroureter and skeletal retardation.

	At 100 mg/kg an increased incidence of hydroureter in the fetuses was observed. No effects were observed in the dams or fetuses at 30 mg/kg. The maternal and developmental NOEL was 30 mg/kg.
Reference:	BASF AG (1993). Unpublished Data (90/88), 09.06.93 (cited in IUCLID (2000). IUCLID Dataset, "1,3-Dimethylurea" (February 19, 2000)).
Reliability:	High because a scientifically defensible or guideline method was used.
Species/Strain:	Rats/Wistar Mice/ICR
Sex/Number:	Female rats/6 Female mice/ 11
Route of Administration:	Gavage
Exposure Period:	Rats: Gestation Day 12 Mice: Gestation Day 10
Frequency of Treatment:	Single oral dose
Exposure Levels:	Rats: 2000 mg/kg Mice: 2000 mg/kg
Method:	Rats and mice at 15 and 8 weeks of age, respectively, were used. They were housed in a controlled environment of 24±1°C and 55±5% relative humidity, maintained on laboratory chow, and given tap water *ad libitum*. Female rats and mice were paired overnight with a male, and were examined the following morning for the presence of vaginal plug (Day 0 of gestation). Aqueous solutions of the test substances were prepared and given orally to female rats by intubation on day 12 of pregnancy, and on day 10 of pregnancy to female mice. Urea and thiourea were used as negative controls. Female rats and mice were killed on days 20 and 18 of pregnancy, respectively. The number of implants and live and dead fetuses were counted. Live fetuses were individually weighed and examined for gross abnormalities, and then divided into 2 groups. One group (derived from the right uterine horn) was processed for skeletal examinations. The other group was fixed in Bouin's and examined for visceral anomalies. Differences in numbers of implants, live fetuses, and fetal body weights were analyzed by the Student's t test. The litter was considered the experimental unit. Differences in

	resorption and malformation incidences, assessed on the basis of number of affected fetuses, were analyzed by the Chi-square test.
GLP:	Unknown
Test Substance:	1,3-Dimethylurea, purity not reported
Results:	1,3-Dimethylurea caused only a decrease in the weight of rat fetuses. In the mouse fetuses, it was observed to produce an increase in fetal resorptions and a decrease in the fetal weights. It also induced cleft palate and fusion of caudal vertebrae in 8 fetuses from 5 dams and in 12 fetuses from 8 dams, respectively.
Reference:	Teramoto S. et al. (1981). Teratology, 23:335-342. Kaneda, M. et al. (1980). Teratology, 22(1):13A.
Reliability:	Medium because a suboptimal study design was used.

Additional References for Developmental Toxicity: None Found.

5.4 Reproductive Toxicity: Isolated Intermediate; Not a Required Endpoint.

5.5 Genetic Toxicity

Type: ***In vitro*** **Bacterial Reverse Mutation Assay:** No Data.

Type: ***In vitro*** **Clastogenicity Studies:** No Data.